Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

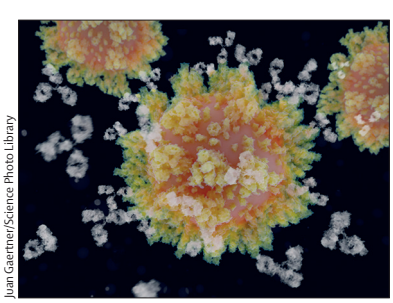
Why the application of IVIG might be beneficial in patients with COVID-19

In *The Lancet Respiratory Medicine*, Aurélien Mazeraud and colleagues showed that the application of intravenous immunoglobulins (IVIGs) in patients with COVID-19-induced moderate-to-severe acute respiratory distress syndrome did not improve clinical outcomes but had a non-significant association with more adverse events.[1]

We would like to address reasons for the lack of effect that were not discussed in Mazeraud and colleagues' Article.

The rationale to apply IVIGs in infectious diseases can be either to target hyperinflammation, to use the anti-infective properties of IVIGs to treat the primary infection, or both. Beyond that, IVIGs might provide protection against secondary infections and thereby reduce morbidity and mortality. First evidence shows that the beneficial effects of IVIGs might depend on the composition of the IVIG preparation, the immune status of the patient, and the severity of the disease.[2]

Concerning the preparation of the IVIG solution, those consisting mainly of IgG (as applied in Mazeraud and colleagues' study) have been shown to have little or no effect in patients with sepsis.[3,4] By contrast, first data published on IgM-enriched IVIG solution are encouraging.[5,6]



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Concerning the immune status of patients, Mazeraud and colleagues did not investigate parameters of immune function. Notably, in several studies, an increased mortality was associated with low baseline serum levels of immunoglobulins, as shown for instance for influenza.[7,8] From a pathophysiological point of view, it would be possible that beneficial effects of a substitution of IVIGs were observed only in these patients, but not in those with normal or elevated baseline immunoglobulin levels.

In this context, we would like to draw attention to a 2018 phase 2 randomised controlled trial in 160 patients with severe community-acquired pneumonia who required invasive mechanical ventilation.[5] In this double-blind study, in addition to standard of care, an IgM-enriched IVIG solution (42 mg IgM/kg per day) was applied. The primary combined endpoint of ventilator-free days and 28-day all-cause mortality was not statistically different in the intention-to-treat cohort (22·2% *vs* 27·8%). Most importantly, in a prespecified subgroup analysis of patients with a high level of inflammation (C-reactive protein concentrations higher than 70 mg/L), low IgM serum levels (lower than 0·8 g/L) or both, mortality was reduced significantly, with the highest level of mortality reduction in the cohort with high C-reactive protein concentrations and low IgM levels.

Therefore, by contrast with the conclusion of Mazeraud and colleagues, we hypothesise that IVIG application in patients with COVID-19 might be beneficial if a specific IgM-enriched IVIG solution is applied in patients with low IgM levels and a high level of inflammation.

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